REMARKS

Claims 5, 8 to 16, 18, 20 to 24 and 27 to 31 as amended and new Claims 54 and 55 are present.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Claim 12 has been amended to define the methacrylic acid copolymer as set out in the Specification at page 8, lines 15 to 17.

Claims 18 and 19 have been combined into Claim 18.

Claim 27 has been amended to define the enteric coating as set out at page 8, lines 15 to 17 of the Specification.

Claims 54 and 55 have been added to cover the inclusion of an alkaline material as set out at page 9, lines 4 to 7 of the Specification.

Claims 5, 9 and 27 have been amended to exclude hydroxypropylmethyl cellulose phthalate from the enteric coating.

During a telephone discussion with the Examiner on December 30, 2004, the Examiner indicated that the subject application could possibly be allowable over U.S. Patent No. 5,225,202 to Hodges et al. if Applicants agree to amending the claims to delete hydroxypropylmethyl cellulose phthalate. Inasmuch as the inventors and other relevant personnel were not available (due to the 2004 Holiday season) for consultation regarding the amendment suggested by the Examiner, the Examiner indicated that she would issue a rejection based on the Hodges et al. patent so that Applicants would have sufficient time to study Hodges et al.

As indicated, Applicants have now amended Claims 5, 9 and 27 to exclude hydroxypropylmethyl cellulose phthalate from polymers used in the enteric coating. Accordingly, it is believed that Claims 5, 9 and 27 as well as Claims 8, 10 to 24 and 28 to 31 which are dependent thereon are patentable over Hodges et al. taken alone or in combination with U.S. Patent No. 5,109,003 to Tanaka et al. (newly cited).

In order to complete the record, Applicants will respond to the Examiner's rejection.

A discussion of Applicants' invention as claimed follows.

The nucleoside analogue 2′,3′-dideoxyinosine (ddI) is a widely prescribed drug in combination with other antiretroviral agents for the treatment of AIDS. In spite of the well established therapeutic effectiveness of ddI in terms of inhibition of HIV replication, the patient compliance for ddI has presented problems. Thus while various formulations of ddI are available, they have been criticized by patients in view of their unpleasant taste and inconvenience in use.

The ddI formulations of the prior art are either chewable/dispersible buffered tablets which must be thoroughly chewed, manually crushed or uniformly dispersed in water prior to administration. Moreover, as ddI is highly acid labile, the prior art formulations, including the chewable/dispersible form and the powder formulation for oral solution, contain buffering agents. In the pediatric form, ddI must be administered in combination with antacids. The buffers and antacids frequently lead to significant gastrointestinal imbalance as noted by sever diarrhea which may in turn impede drug absorption.

Patients have also complained about chewing the very large ddI tablets as well as the unpleasant taste of ddI and the bitter and chalky taste of buffers. This also applies to the oral solutions of ddI which must be dispersed in a large volume of water, which, moreover, is very time consuming.

All of the above factors impede the patients regular intake of the drug. Particularly in case of HIV or AIDS patients medication non-compliance may have a very serious impact on the course of the disease. There has thus been a great need for a ddI formulation which is simple to use and without the aforementioned problems and thus readily acceptable to the patient.

In spite of the fact that the antiviral agent ddI has been available for a very long time, it was not until the present invention that a formulation was developed which is readily acceptable to the patient.

As set out in the claims as amended the problems associated with the prior art ddI formulations could be avoided by formulating the active ingredient ddI at a higher drug load (80 to 100%) in enteric-coated beadlets. The enteric coating of the beadlets is devoid of hydroxypropylmethyl cellulose phthalate. In addition, use of the enteric coating enables the enteric-coated beadlets to be devoid of a protective coat between the core and the enteric coating of the beadlet.

In light of the multitude of possible excipients, carriers, coatings as well as dosage forms available, the person of skill in the art could not have arrived at the instant solution by a mere consideration of the prior art, particularly taking into account the special physicochemical properties of ddI as well as its pharmacodynamic profile.

Claims 5, 8 to 24 and 27 to 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hodges et al. (US 5,225,202), in view of Tanaka et al. (US 5,109,003).

The Examiner contends that

> "Hodges teaches coated pellets composition comprising drug-containing core, and an enteric coating layer surrounding the core, wherein the enteric coating will provide protection of the medicament at pH less than 3, but will allow for drug release at a pH of 4.5 or higher (see abstract; column 2, lines 35-53; and column 3, lines 10-15). Drug in the core is an acid labile drug includes dideoxyinosine (ddI) (column 3, lines 16-19). The core further comprising one or more disintegrants such as sodium starch glycolate, corn starch, or cross-linked polyvinylpyrrolidone in an amount of from about 2 to about 15%; and binder in an amount of from 0 to about 20% (column 3, lines 20-26, 54-64). The enteric coating layer comprising hydroxypropylmethyl cellulose phthalate (HPMCP); plasticizer such as diethyl phthalate, triethyl citrate, or polyethylene glycol; and anti-adherent such as talc, magnesium stearate, or fumed silica (column 4, lines 17-51). The coated pellets may be filled into hard shell capsule (column 6, lines 3-4). Hodges teaches the subcoat layer between the core and outer enteric coating layer. However, Hodges discloses that the subcoat layer *may* be needed only where the core includes a drug which is incompatible with the enteric coating layer (column 4, lines 59-65). It is noted that all of Hodges' examples that include the subcoat layer show the use of pravastatin as the active agent. None of the examples show subcoat layer used in ddI composition.
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> Hodges does not explicitly teach the amounts of the ingredients, as well as sodium carboxymethylcellulose as a binder, and methacrylic acid being the enteric coating polymer. However, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Regarding sodium carboxymethylcellulose, and methacrylic acid copolymers, it is the position of the examiner that sodium carboxymethylcellulose is a well known binder, and methacrylic acid copolymer is a well known enteric coating polymer. However, to be more specific, Tanaka is cited, wherein Tanaka teaches an enteric coating composition comprising binder such as sodium carboxymethylcellulose, and enteric coating polymer includes HPMCP or methacrylic acid copolymers (column 5, lines 46-64). Thus, it would have been obvious for one of ordinary skill in the art to modify the coated pellets composition of Hodges using sodium carboxymethylcellulose as the binder, and methacrylic acid

copolymers as the enteric coating polymer in view of the teaching of Tanaka, because Tanaka teaches an enteric coating composition comprising a well known binder and a well known enteric coating polymer such as HPMCP and methacrylic acid copolymers, and because Hodges teaches an enteric coated pellets composition that has good resistance to deterioration at pH less than 3 but have good drug release properties at greater than 3."

It is submitted that Applicants' beadlet formulation as claimed in Claims 5, 6 to 16, 18, 20 to 24, 27 to 31, and 53 and 54 is patentable over Hodges et al. taken with Tanaka et al.

U.S. Patent No. 5,225,202 to Hodges et al. discloses a pharmaceutical composition which includes a core containing

(1) a medicament which is sensitive to a low pH environment, such as pravastatin or 2′,3′-dideoxyinosine,

(2) a buffering agent to raise pH to ensure rapid drug release between pH's 4 and 5 and to aid in minimizing drug degradation in the core due to acid ingress in low pH environments (Col. 3, lines 6 to 9); and

(3) an enteric coating, which includes a neutralized form of hydroxypropylmethyl cellulose phthalate, and a plasticizer.

In Col. 4, starting at line 59, Hodges et al. states that

"where the core includes a drug which is incompatible with the enteric coating layer, a subcoat layer which acts as a physical barrier between the core and outer enteric coating layer will be employed."

Since the drug ddI is incompatible with the enteric coating layer, Hodges et al. will have to employ a subcoat layer. It is not optional under these circumstances.

Hodges et al. will include a binder in the core which, as disclosed in Col. 3, lines 58 to 65, is polyvinylpyrrolidone, lactose, starches such as corn starch, modified corn starch, sugars, gum acacia, or a wax binder such as carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax.

It is submitted that Applicants' pharmaceutical composition as now claimed is patentable over Hodges et al. for the following reasons:

(1) Applicants' core does not include a buffering agent as required by Hodges et al.

(2) Applicants do not include a subcoat layer as would be requested by Hodges et al. where the drug is 2′,3′-dideoxyinosine since in Applicants' composition there is no incompatibility between the 2′,3′-dideoxyinosine and the enteric coating.

(3) Applicants use a different binding agent than Hodges et al.

(4) Applicants use an enteric coating which does not include hydroxypropylmethyl cellulose phthalate which is required in Hodges et al.

In view of the above differences, which differs are unobvious, it is submitted the Applicants' composition as claimed is patentable over Hodges et al.

U.S. Patent No. 5,109,003 to Tanaka et al. discloses enteric-coated tablets or granules containing a peptic ulcer drug, which enteric coating may include HPMCP or methacrylic acid copolymers.

Applicants' invention as claimed is directed to enteric-coated beadlets and not an enteric-coated tablet or granule as disclosed by Tanaka et al.

Applicants' enteric coated beadlets include 2′,3′-dideoxyinosine and not an ulcer drug as in Tanaka et al.

Thus, it is seen that the very nature and inventive concept of Tanaka et al. is totally different from Applicants' composition as claimed. Thus, it is submitted that Applicants' composition as claimed is patentable over Tanaka et al.

Applicants' composition as claimed is clearly patentable over a combination of Hodges et al. and Tanaka et al.

Hodges et al. requires an enteric coating which includes hydroxypropylmethyl cellulose phthalate and a protective subcoat, both of which are excluded from Applicants' beadlets as claimed.

Tanaka et al. does not relate to beadlets. The technology of enteric-coated tablets or granules is different from beadlets. In fact, absent the use of hindsight in view of Applicants' disclosure, one skilled in the art would have no reason to combine the teachings of Hodges et al. and Tanaka et al. Therefore, the combination of these references is improper and should be withdrawn. Regardless, the above combination of references does not make Applicants' beadlets as claimed obvious for the reasons set out above.

WO 97/25066 A1 (DePui et al.) has been cited of interest as teaching an "enteric coated composition for acid labile active agent, such as proton pump inhibitor."

There is no disclosure or suggestion in DePui et al. taken alone or in combination with Hodges et al. or Tanaka et al. of Applicants' invention as claimed.

In view of the foregoing, it is believed that Claims 5, 8 to 16, 20 to 24, 27 to 31, and 53 and 54 are in condition for allowance.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

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Burton Rodney
Attorney for Applicants
Reg. No. 22,076